

# **Effects of oversulfated and fucosylated chondroitin sulfates on coagulation. Challenges for studies of anticoagulant polysaccharides**

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We report the effects of a chemically oversulfated chondroitin sulfate and a naturally fucosylated chondroitin sulfate on the coagulation system. Oversulfated chondroitin sulfate is a contaminant of heparin preparations with severe side effects. Fucosylated chondroitin sulfate has been proposed as alternative anticoagulant. These highly sulfated chondroitin sulfates differ significantly in their effects on coagulation. They have a serpin-independent anticoagulant activity, which preponderates on plasma system. They have also a serpin-dependent anticoagulant activity but differ significantly on the target coagulation protease and preferential serpin. Their anticoagulant effects differ even more markedly when tested as inhibitors of coagulation proteases using plasma as a source of serpins. Possibly, the difference is a consequence of high bioavailability of fucosylated chondroitin sulfate while oversulfated chondroitin sulfate has strong unspecific binding to plasma protein and low availability for the binding to serpins. Fucosylated chondroitin sulfate, but not oversulfated chondroitin sulfate, has antithrombotic effect when tested using a venous thrombosis experimental model. These chondroitin sulfates produce approximately the same effects on in vitro assays of factor XII activation, based on bradykinin generation. However, only fucosylated chondroitin sulfate induces hypotension and decreases heart rate when intravenously injected into rats. In conclusion, the complexity of the regulatory mechanisms involved in the action of highly sulfated polysaccharides in coagulation requires their analysis by a combination of in vitro and in vivo assays. Our results are relevant in face of the pressing need for new anticoagulant drugs or alternative sources of heparin.